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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,519	11/10/2003	James M. Robl	50195/023003	4828

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,519	ROBL ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-25,28-32 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *9-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 25, 28-32 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 4, 2006 has been entered.

The declaration by James M. Robl filed June 4, 2006 has been considered but is not persuasive for reasons set forth below. The declaration filed June 12, 2007 by Dr. Yoshimi Kuroiwa and applicant's arguments filed June 4, 2007 is not persuasive for overcoming the rejection made in the office actions mailed June 12, 2006 and December 1, 2006 under 35 U.S.C. § 102 (e).

The restriction of groups I, II and III, set for in the office action mailed April 10, 2006, is withdrawn. Claims 7 and 8 are examined in this office action.

Pending claims are 1, 4-25, 28-32 and 35-38 Claims under examination are 1, 4-8, 25, 28-32 and 35-38. Claims 9-24 are withdrawn from consideration.

The declaration filed June 12, 2007 by Dr. Yoshimi Kuroiwa and applicant's arguments filed June 4, 2007 are persuasive for the withdrawal of the rejection made in the office action mailed December 1, 2006 under 35 U.S.C. § 112, enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 7 are to a transgenic bovine whose genome comprises a STOP codon into one or both of its prion alleles, where the bovine fails to produce functional prion protein.

The claims are not enabled because a human prion disease is known in the art to be associated with an improper termination codon, an amber codon, inserted by a naturally occurring mutation of the human endogenous prion gene (Muramoto, page 753, col. 1, parag. 3, lines 1-3). Thus, it is unpredictable that a bovine produced through the insertion of a STOP codon in its prion gene will be prion disease free. This is particularly the case as spongiform encephalitis is known to naturally occur in bovines. Thus a human mutant associated with human disease may cause BSE in a transgenic bovine comprising the human mutation or a similar mutation at any location in the prion coding sequence. It is known that a mutant prion protein is required for infectivity (Aguzzi, page764, col. 1, parag. 1). Therefore, at the time of the present invention, the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to produce a BSE-free bovine whose genome comprised a STOP codon in its prion gene coding sequence.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The location of the cell of claims 25 and 28-31 is not clear. If applicant means "isolated," the claims so be so amended. Otherwise, it is not clear how one can claim a part of a whole product.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 6, 8, 25, 28-30, 32, 35 and 36 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by US 2002/0069423 (Good) for reasons set forth in the office action mailed June 12, 2006 and December 1, 2006.

Good teaches heterozygous and homozygous bovines comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion gene, where the bovines lack functional prion protein (page 6, parag. 0052, lines 1-4, page 18, parag. 00196 and page 19, parag. 0208).

Good also teaches a bovine fetal fibroblast comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion protein gene and deletion of prion sequence, where function prion protein is not expressed (page 7, parag. 0074, lines 1-3; page 8, parag. 0091; page 9, parag. 0097, lines 16-20 and parag. 0098, lines 1-4; and page 16, parag. 0165-0169). Also Good states to produce a homozygous disrupted prion bovine embryonic fibroblast, fibroblasts will be isolated from a heterozygous bovine fetus and targeted a second time, if necessary, with a targeting vector containing a different selection maker (parag. [0201], lines 5-8; parag. [0204] and parag. [0206], lines 11-13).

Good teaches a method for producing a transgenic bovine cell having reduced expression of function prion protein comprising introducing into a first prion gene the insertion of positive selection marker targeting vector into a bovine fetal fibroblast under

conditions that allow homologous recombination to produce a fibroblast having a hemizygous mutation and a homozygous mutation (page 16, parag. 0164-0167).

Good teaches the production of a transgenic bovine having reduced expression of functional prion protein comprising inserting a fetal fibroblast cell or it nucleus into an enucleated oocyte, wherein said cell comprises an insertion of a positive selection marker into a prion protein allele, transferring the oocyte to a surrogate mother and permitting term development (page 18, parag. 0184-0196).

Applicant argues that declarant Robl provides reasons why Good is not enabled. Applicant argues Good fails entirely to report the production of either heterozygous of homozygous PrP knockout bovine cells or bovines. Applicant argues Dr. Kuroiwa states Good failed in its actual attempts to produce PrP knockout cells (parag. 3) and provides insufficient prophetic guidance to do so (parag. 3). Applicant argues Dr. Robl states one of skill in the art would not be able to produce reproducibly a PrP knockout cell of bovine (parag. 2). Applicant states Dr. Robl states Good provides a single prophetic method where bovine fetal fibroblasts are electroporated with a targeting vector and plated at a density of 500,000 cells/100 mm^2 plate. Selected colonies are to be isolated using cloning rings. Applicant argues Dr. Robl states the method disclosed in Good would not be successful because 1) only a fraction of the cell fibroblasts would have been correctly targeted; the plating density is too high to allow for efficient isolation of individual colonies as the cells would be essentially confluent; fibroblasts are motile cells and not amenable to be isolated using cloning rings; and there would be no guarantee that fetuses produced would be transgenic as the donor cell population would be a mixture of targeted and non-targeted cells. These arguments are not persuasive.

Reduction to practice, for patentability, does not mean the claimed invention is actually produced. Thus, an applicant need not make the invention they are claiming; Good

need not actually produce PrP knockout bovines in order to anticipate the presently claimed invention. Commentary on Good cannot be found in either Kuroiwa declaration. With regard to the statements made by Dr. Robl, at the time of filing, transfected fetal fibroblasts had been isolated in the art by culturing transfected fibroblasts in the presence of selection medium followed by isolation with cloning rings (page 190. col. 1, parag. 2, lines 10-24). Good discloses this same method: selection, which would kill some number of cells that had not been transfected with the targeting construct, followed by isolation with cloning rings (Good, [0167]-[0169]). Thus the density of the fibroblast cell population would be reduced, and the transfected fibroblasts could be isolated. The method Good, contrary to declarant's opinion, would reasonably provide bovine fetal fibroblasts having a disrupted PrP gene. Further, even if Good's method isn't efficient, all there needs to be is one bovine fetal fibroblast containing a nonfunctional PrP gene, which can then be grown to produce a cell line. The cell line can then be used in nuclear transfer methods to produce a cloned bovine.

Applicant further argues Declarant Robl states Good's proposed primary screening method for identifying targeted prion knockout cells is incompatible with fibroblasts because fibroblast senesce. Applicant argues Good does not provide methods to obtain sufficient DNA from colonies to perform PCR followed by Southern blotting. Applicant argues the method requires many population doublings leaving few cells for expansion. Declarant Robl states the fibroblasts would senesce before sufficient DNA could be extracted. Further applicant argues no other screening methods are taught by Good. These arguments are not persuasive.

Good ([169]) states for each positive colony, two cultures are produced; one for PCR and Southern analysis and one for freezing cell stocks. Others have grown targeted fibroblasts, performed PCR and confirmed the PCR results by Southern blot analysis (Dai, page 252, col. 1, parag. 1 to col. 2, through parag. 1). It also noted at the time of filing

other means for identifying properly targeted fibroblasts were known. For example, sequence of PCR products was known (Zheng, page 8069, col. 1, parag. 4). The specification need not teach methods known in the art. One of ordinary skill in the art could have used any method of identifying targeted fibroblasts available. There is no requirement that only the method of Good be used for enablement of the specification. In view of Dai and Zheng, fibroblast senesce does not prevent identification of properly targeted cells.

Applicant argues Declarant Robl states Good's cells could not survive freezing because they are near senescence. This argument is not persuasive.

Freezing of the cells is not required for the nuclear transfer method. The freezing of cells is to provide a backup source of cells if needed for further experimentation.

Applicant argues Good provides in sufficient guidance for the second targeting step, which is necessary to produce homozygous knockout cows. Applicant argues Good notes a second targeting is unpredictable as the second vector often recombines with the previously targeted allele and use of the same selection marker will not distinguish between heterozygous and homozygous cells. Applicant argues Good does suggest use of a second marker to determine whether the second vector has been successfully incorporated into a cell, but Good fails to provide any guidance on how to prevent retargeting of the first allele. These arguments are not persuasive.

It is possible, that the second targeting vector will insert at the second prion locus. Thus, cells that are resistant to both antibiotics would have a reasonable expectation of having both loci targeted. What applicant needs to provide is evidence, arguments or reasoning that the method of Good would never provide a homozygous prion knockout fibroblast.

Applicant argues that *In re LeGrice* states "descriptions .. in order to bar issuance of a patent, must be capable, when taken in conjunction with the knowledge to those skilled in

the art to which they pertain, of placing the invention in the possession of those so skilled." Good meets the criteria set forth in LeGrice. While experimentation may be required to implement the disclosure of Good, it has not been established on this record that such experimentation does not have a reasonable expectation of success.

Applicant argues, the method disclosed in the present specification is distinct from that of Good. In particular, applicant argues, the disclosed method teaches the dilution plating of 10,000,000 electroporated cells into 60, 24-well plates, resulting in a much lower density of cells compared to Good, allowing formation of individual colonies. Applicant also argues the specification provides a PCR-based screening method for targeted integrations that does not rely on Southern blotting, as such the method does not require the multiple population doublings to produce sufficient DNA. Applicant argues the specification provides two targeting vectors, on with a neomycin resistance gene and the other with a promising resistance gene to produce homozygous prion knockout fibroblasts. These arguments are not persuasive.

While these methods are undisputedly disclosed in the present specification, the are not part of the claims. Thus, Good anticipates the breadth of applicant's claimed invention. Further, applicant has stated the methods of Good are not enabled. Thus, applicant's claims are not enabled as they encompass those of Good. However, until applicant's method claims contain the methods steps argued, they remain rejected by Good.

Applicant's notation regarding the prosecution of Good has been reviewed. The issue, if applicant's claims encompass those of Good, and applicant's claims are eventually found allowable, then those of Good should also be found allowable. The course of action maybe, once allowable claims are found in the present application, to suspend prosecution until Good is ready for allowance.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0069423 (Good) in view of Muramoto et al. (1997) Nature Med., Vol. 3, pp. 750-755.

Good teaches heterozygous and homozygous bovines comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion gene and deletion of prion sequence, where the bovines lack functional prion protein (page 6, parag. 0052, lines 1-4; page 7, parag. 0074, lines 1-3; page 8, parag. 0091; page 9, parag. 0097, lines 16-20 and parag. 0098, lines 1-4; and page 16, parag. 0165-0169 page 18, parag. 00196 and page 19, parag. 0208).

Good also teaches a bovine fetal fibroblast comprising an insertion of a positive selection marker into one or both alleles of an endogenous prion protein gene and deletion of prion sequence, where function prion protein is not expressed (page 7, parag. 0074, lines 1-3; page 8, parag. 0091; page 9, parag. 0097, lines 16-20 and parag. 0098, lines 1-4; and page 16, parag. 0165-0169).

While Good does not specifically teach the disruption of a prion genomic sequence in bovines through insertion of a STOP codon, such was known in the art. Muramoto teaches the production of transgenic mice whose genomes comprises an insertion of a STOP codon through the conversion of codon 145 to a tyrosine (page 753, col. 1, parag.3, lines 3-7). The mice failed to produce PrP or symptoms of prion disease (page 753, col. 1, parag. 4, lines 3-8.

Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to make prion deficient bovines as claimed where expression of the prion protein was inhibited by the insertion of a STOP codon into the prion genome given the teaching of Good of producing a prion deficient bovine by disruption of the endogenous prion gene, and Muramoto teaching prion deficient transgenic mice having a STOP codon inserted into their prion gene.

Claims 25, 31, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0069423 (Good) in view of 20030046722 (Collas).

Good teaches a method for producing by nuclear transfer a transgenic bovine having reduced expression of function prion protein comprising inserting a diploid cell into an enucleated MII oocyte where the cell comprising a positive selection marker and a prion gene disrupting sequence, transferring the oocyte or an embryo formed from said oocyte into the uterus of a host bovine under conditions that allow said oocyte or said embryo to develop into a fetus, where the genome of the fetus comprises the disruption and produces reduced levels of function prion protein (parags. [0182], [0184], [0186], [0188], [0190] and [0192]). However, Good does not teach permeabilizing nuclear donor cells for nuclear transfer.

Collas teaches cell permeabilized with digitonin or Streptolysin ([0133]). The permeabilized cells are then transferred into an oocyte for nuclear transfer ([0162]. Collas states permeabilized cells are more efficiently cloned (parag. [0003], lines 1-2).

Further, the isolation of any cell type would have been obvious to the ordinary artisan at the time of filing.

Thus, at the time of instant invention it would have been obvious to ordinary artisan to modify the method of Good by permeabilizing the donor cells to increase cloning efficiency.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

August 6, 2007